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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,400	COLLINS ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *9-14,20-24,27-54 and 57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,15-19,25,26,55 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 June 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6-16-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of group IV, claims 1-8, 15-19, 25, 26, 55 and 56, in the reply filed on 11-27-06 is acknowledged. The traversal is on the ground(s) that each of groups I-IX is a different species of attenuating mutation. Groups IV-VI should be rejoined. Either or both groups I and II should be rejoined with group III. Groups IX and X should be rejoined. Group XI should be rejoined with elected group and group XIII should be rejoined similarly. This is not found persuasive because groups I-X and XII are drawn to different rHMPVs having different gene sequences or genomic structures that could result in dramatically different phenotype of said rHMPVs. SH ORF, G ORF, M2-1 ORF and M2-2 ORF and their mutants represent different genes encoding different proteins having different biological functions. Different order and number of copies of genes could result in dramatically different function and phenotype of the rHMPVs. Therefore, those different rHMPVs can be used in different mode of operation and have different functions. They do not overlap in scope. Inventions XI and inventions I-X and XII are related as product and process of use. In the instant case the rHMPV in inventions I-X and XII can be used to produce a recombinant protein in vitro or to screen an antiviral compound in immunoassay as opposed to induce an immune response in a subject. Thus, groups XI and groups I-X, XII are patentably distinct from each other. Similarly, the rHMPV in inventions I-X and XII can be used to produce a recombinant protein in vitro or to induce an immune response in a subject as opposed to screen an antiviral compound in immunoassay. Thus, groups XIII and groups I-X, XII are patentably distinct from each other. Thus, groups I-XIII are not just different species, they are patentably distinct inventions from each other.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 9-14, 20-24, 27-54 and 57 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11-27-06.

Applicants' preliminary amendment filed 6-16-04 has been entered. Claims 46-57 have been amended to correct the claim number. Claims 1-57 are pending. Claims 1-8, 15-19, 25, 26, 55 and 56, and rHMPV comprising one or more attenuating nucleotide modification or comprising one or more nucleotide substitution that reduces or ablates expression of rHMPV M2-2 ORF, are under consideration.

Double Patenting

3. Claim 8 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 18. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Only rHMPV M2-2 ORF is considered in claim 8, therefore, claims 8 and 18 are duplicate claims.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 6, 25, 55 and 56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "wherein the detectable heterologous sequence is operably linked to HMPV transcription gene start and gene end signals" in claim 6 is vague and renders the claim indefinite. There are about 12 different genes within HMPV genome. It is unclear which gene start and gene end signals are intended.

The phrase "wherein the phenotypic change comprises at least one of a change in growth properties in cell culture ..., or a change in immunogenicity" in claim 25 is vague and renders the claim indefinite. It is unclear whether the "at least one of a change" includes "a change in immunogenicity" or not. Changing the phrase to "wherein the phenotypic change comprises at least one of a change selected from the group consisting of a change ..., and a change in immunogenicity" would be remedial.

The phrase "comprising an operably linked transcriptional promoter" in claim 55 is vague and renders the claim indefinite. It is unclear what the transcriptional promoter is operably linked to. Claim 56 depends from claim 55 but fails to clarify the indefiniteness.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-8, 15-19, 25, 26, 55 and 56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims read on any recombinant human metapneumovirus (rHMPV) comprising a partial or complete recombinant HMPV genome or antigenome comprising one or more attenuating nucleotide modification comprising a partial or complete deletion of M2-2 ORF or one or more nucleotide substitution that reduces or ablates expression of the M2-2 ORF, and a N protein, a P protein and a L protein that are derived from any virus or any source. The claims encompass a genus of various rHMPV strains and substrains having different nucleotide sequences.

The specification only discloses the nucleotide sequence of HMPV strain 83 (SEQ ID No. 1) and HMPV strain 75 (SEQ ID No. 2). The claims encompass a genus of structural variants of SEQ ID No. 1 or 2, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification fails to provide the structural features of the variants that one skilled in the art can envision the nucleotide sequence of any other HMPV strain or substrain. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. The nucleotide sequences of SEQ ID Nos. 1 and 2 are insufficient to describe the claimed recombinant HMPVs.

The claims also read on one or more attenuating modification comprising deleting or substituting the nucleotide sequence of M2-2 ORF of any HMPV. The modified nucleotide sequence of M2-2 ORF of any HMPV could differ dramatically from the disclosed M2-2 ORF sequence, and said modified nucleotide sequence could encode dramatically different amino acid sequences or not encode any amino acid sequence at all. The claims encompass various modified nucleotide sequences encoding a genus of numerous structural variants of the amino acid sequence encoded by the disclosed M2-2 ORF, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification fails to provide the structural features of the variant proteins and the biological function of the variant proteins was unpredictable at the time of the invention (discussed below). The specification also fails to provide guidance for whether those variant proteins could result in the phenotypic change as recited in the claims. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the amino acid sequence encoded by the M2-2 ORF as disclosed in the present application is insufficient to describe the genus. The nucleotide sequence of the disclosed M2-2 ORF is insufficient to describe the claimed recombinant HMPVs.

This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed recombinant HMPVs and expression vector

comprising said HMPVs. Thus, it is concluded that the written description requirement is not satisfied for the recombinant HMPVs and expression vector comprising said HMPVs as claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieve regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the disclosed sequences referred to above, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is

reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

8. Claims 1-8, 15-19, 25, 26, 55 and 56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the recombinant HMPV lacking M2-2 ORF as disclosed in the specification, does not reasonably provide enablement for any recombinant human metapneumovirus (rHMPV) comprising a partial or complete recombinant HMPV genome or antigenome comprising one or more attenuating nucleotide modification comprising a partial or complete deletion of M2-2 ORF or one or more nucleotide substitution that reduces or ablates expression of the M2-2 ORF, and a N protein, a P protein and a L protein that are derived from any virus or any source, wherein said rHMPV results in the phenotypic change recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-8, 15-19, 25 and 26 are directed to an isolated recombinant human metapneumovirus (rHMPV) comprising a partial or complete recombinant HMPV genome or antigenome comprising one or more attenuating nucleotide modification comprising a partial or complete deletion of M2-2 ORF or one or more nucleotide substitution that reduces or ablates expression of the M2-2 ORF, and a N protein, a P protein and a L protein. Claims 3 and 4 specify the recombinant HMPV genome or antigenome further comprises a detectable heterologous sequence endogen a polypeptide, such as a reporter. Claim 5 specifies the reporter comprises GFP. Claim 6 specifies the detectable heterologous sequence is operably linked to

HMPV transcription gene start and gene end signal. Claim 8 specifies the M2-2 functional protein is not produced. Claims 15 and 16 specify the one or more attenuating nucleotide modifications comprises one or more nucleotide substitution that reduces or ablates expression of a rHMPV M2-2 ORF or further comprises one or more substitution that ablates one or more potential translation initiation codons of the rHMPV M2-2 ORF or introduces one or more in-frame stop codons into the rHMPV M2-2 ORF. Claims 17 and 19 specify the rHMPV sequence of SEQ ID No. 1 and rHMPV M2-2 ORF of SEQ ID No. 1, respectively. Claim 25 specifies the one or more attenuating nucleotide modifications produce the recited desired phenotypic change in the rHMPV. Claims 55 and 56 are directed to an expression vector comprising an operably linked transcriptional promoter, a partial or complete recombinant rHMPV genome or antigenome, and a transcriptional terminator, wherein the rHMPV genome or antigenome comprises one or more attenuating nucleotide modifications.

The specification only discloses the nucleotide sequence of HMPV strain 83 (SEQ ID No. 1) and HMPV strain 75 (SEQ ID No. 2) (e.g. p. 16). The specification discloses that the rHMPV lacking M2-2 ORF (ΔM2-2) replicates more than 10-fold less efficiently than wild type HMPV in LLC-MK2 cells, however, in Vero cells the ΔM2-2 mutant grows to a final titer that equals or exceeds that of wild type HMPV. One important difference between LLC-MK2 and Vero cells is that the latter lack the structural genes for type I interferon. The ΔM2-2 mutant HMPV is more sensitive to interferon as compared to wild type rHMPV-GFP (e.g. p. 79-80). The claims read on any recombinant human metapneumovirus (rHMPV) comprising a partial or complete recombinant HMPV genome or antigenome comprising one or more attenuating nucleotide modification comprising a partial or complete deletion of M2-2 ORF or one or more

nucleotide substitution that reduces or ablates expression of the M2-2 ORF, and a N protein, a P protein and a L protein that are derived from any virus or any source. The claims encompass various rHMPV strains and substrains comprising one or more attenuating modification comprising deleting or substituting the nucleotide sequence of M2-2 ORF of any HMPV. The modified nucleotide sequence of M2-2 ORF of any HMPV could differ dramatically from the disclosed M2-2 ORF sequence, and said modified nucleotide sequence could encode dramatically different amino acid sequences or not encode any amino acid sequence at all. The specification fails to provide adequate guidance and evidence for the biological functions of various variant M2-2 proteins encoded by the modified M2-2 ORF sequence comprising one or more attenuating nucleotide modification comprising a partial or complete deletion of M2-2 ORF or one or more nucleotide substitution that reduces or ablates expression of the M2-2 ORF, and whether and what kind of phenotypic change of the rHMPV could be resulted by said modification.

It was known in the art that the amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Rudinger, 1976 (Peptide Hormones, Edited by Parsons, University Park Press, Baltimore, p. 1-7), points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid

substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding" (e.g. Title). In addition, Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). Therefore, biological function of a protein was unpredictable from mere amino acid sequence at the time of the invention. The specification fails to provide adequate guidance and evidence for the biological function of various M2-2 variant proteins and fails to provide specific guidance for whether and how those various modifications of M2-2 ORF would result in any phenotypic change or the claimed phenotypic change of rHMPV in vitro or in vivo. In view of the unpredictable biological function of a protein from mere amino acid sequence and the lack of guidance regarding the phenotypic change of the rHMPV resulted from various modifications of M2-2 ORF, one skilled in the art at the time of the invention would not know how to use the full scope of the claimed rHMPVs in vitro or in vivo.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the level of ordinary skill which

is high, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-4, 6-8, 15, 16, 18, 25, 55 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bermingham et al., 1999 (PNAS, Vol. 96, pp. 11259-11264, IDS) in view of van den Hoogen et al., 2001 (Nature Medicine, Vol. 7, No. 6, p. 719-724, IDS) and van den Hoogen et al., 2002 (Virology, Vol. 295, p. 119-132, IDS).

Claims 1-4, 6-8, 15, 16, 18 and 25 are directed to an isolated recombinant human metapneumovirus (rHMPV) comprising a partial or complete recombinant HMPV genome or antigenome comprising one or more attenuating nucleotide modification comprising a partial or

complete deletion of M2-2 ORF or one or more nucleotide substitution that reduces or ablates expression of the M2-2 ORF, and a N protein, a P protein and a L protein. Claims 3 and 4 specify the recombinant HMPV genome or antigenome further comprises a detectable heterologous sequence endogen a polypeptide, such as a reporter. Claim 6 specifies the detectable heterologous sequence is operably linked to HMPV transcription gene start and gene end signal. Claim 8 specifies the M2-2 functional protein is not produced. Claims 15 and 16 specify the one or more attenuating nucleotide modifications comprises one or more nucleotide substitution that reduces or ablates expression of a rHMPV M2-2 ORF or further comprises one or more substitution that ablates one or more potential translation initiation codons of the rHMPV M2-2 ORF or introduces one or more in-frame stop codons into the rHMPV M2-2 ORF. Claim 25 specifies the one or more attenuating nucleotide modifications produce the recited desired phenotypic change in the rHMPV. Claims 55 and 56 are directed to an expression vector comprising an operably linked transcriptional promoter, a partial or complete recombinant rHMPV genome or antigenome, and a transcriptional terminator, wherein the rHMPV genome or antigenome comprises one or more attenuating nucleotide modifications.

Bermingham teaches construction of the NdeI and K5 mutations, which interrupt M2 ORF2, of human respiratory syncytial virus (hRSV) by adding 2 nucleotides to codon 47 of M2-2 that results in 18 additional codons encoding non-M2-2 amino acids (NdeI mutation), and by changing codon 1, 3 and 7 of M2-2 ORF to ACG and introducing stop codons into all three reading frames immediately downstream of the M2-1 termination codon (K5 mutation) (e.g. Figure 1). The RSV transcription and RNA replication were studied by using a negative-sense RSV-chloramphenicol acetyltransferase (CAT) minigenome C2 containing the CAT ORF under

the control of RSV transcription initiation and termination signals flanked by 3'-leader and 5'trailer regions of the RSV genome (e.g. p. 11260, right column, last paragraph). The minigenome C2 directs the synthesis of antigenome and CAT mRNA when it is complemented by N, P, and L. Bermingham shows that viable RSV was recovered in vitro even when expression of M2-2 is ablated. "Virus lacking M2-2 grew less efficiently than did the wild-type parent in vitro, with titers that were reduced 1,000-fold during the initial 2-5 days, and 10-fold by days 7-8. Compared with wild-type virus, the intracellular accumulation of RNA by M2-2 knockout virus was reduced 3- to 4-fold or more for genomic RNA and increased 2- to 4-fold or more for mRNA". Bermingham suggests that M2-2 mediates a regulatory "switch" from transcription to RNA replication and the M2-2 knockout virus has a highly desirable phenotype for vaccine development because the virus growth is attenuated while gene expression is concomitantly increased (e.g. abstract).

Bermingham does not teach the nucleotide sequence of human metapneumovirus (hMPV).

van den Hoogen (2001) teaches isolation and identification of human metapneumovirus and discloses the nucleotide sequence and amino acid sequences of the HMPV (e.g. abstract, Figure 3, p. 724, left column).

Van den Hoogen (2002) teaches that the clinical symptoms of human respiratory syncytial virus (human RSV) and human metapneumovirus (hMPV) are largely similar to the respiratory tract illnesses, and both hMPV and human RSV are members of Pneumovirinae subfamily (e.g. p. 119, left column).

It would have been obvious for one of ordinary skill in the art at the time of the invention to construct a recombinant HMPV or an expression vector having a partial or complete HMPV genome or antigenome comprising one or more attenuating nucleotide modification as claimed because Bermingham teaches construction of such recombinant human RSV and van den Hoogen teaches the nucleotide sequence of HMPV, and both human RSV and HMPV are members of Pneumovirinae subfamily and clinical symptoms for human RSV and HMPV are largely similar. CAT gene is a type of reporter gene.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to generate a M2-2 knockout virus for vaccine development as taught by Bermingham with reasonable expectation f success.

12. Claims 1 and 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bermingham et al., 1999 (PNAS, Vol. 96, pp. 11259-11264, IDS) in view of van den Hoogen et al., 2001 (Nature Medicine, Vol. 7, No. 6, p. 719-724, IDS) and van den Hoogen et al., 2002 (Virology, Vol. 295, p. 119-132, IDS) as applied to claims 1-4, 6-8, 15, 16, 18, 25, 55 and 56 above, and further in view of Ludin et al., 1996 (Gene, Vol. 173, p. 107-111).

Claims 1 and 3-5 are directed to an isolated recombinant human metapneumovirus (rHMPV) comprising a partial or complete recombinant HMPV genome or antigenome comprising one or more attenuating nucleotide modification comprising a partial or complete deletion of M2-2 ORF, and a N protein, a P protein, and a L protein. Claims 3 and 4 specify the recombinant HMPV genome or antigenome further comprises a detectable heterologous

sequence endogen a polypeptide, such as a reporter. Claim 5 specifies the reporter comprises green fluorescent protein (GFP).

The teachings of Bermingham, van den Hoogen (2001) and van den Hoogen (2002) are as discussed above.

Bermingham, van den Hoogen (2001) and van den Hoogen (2002) do not teach using green fluorescent protein (GFP) as a marker protein.

Ludin teaches preparation of novel vectors expressing fusion protein GFP-MAP2 or GFP-Tau34, which are fluorescent and both MAP2 and Tau34 are functional, to produce fluorescently tagged polypeptide for analysis of the function of those two microtubule-associated proteins and dynamic events in living cells (e.g. abstract).

It would have been obvious for one of ordinary skill in the art at the time of the invention to generate a recombinant HMPV expressing a GFP as a marker or a reporter because Ludin teaches preparation of novel vectors expressing GFP as a marker for analysis of the function and dynamic events in living cells.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to monitor the function of the fusion protein or dynamic events in living cells as taught by Ludin with reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER